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④ COMPOUNDS OF S-TRIAZINE DERIVATIVES AND THEIR SALTS AND PROCESS FOR PRODUCTION OF SAID COMPOUNDS

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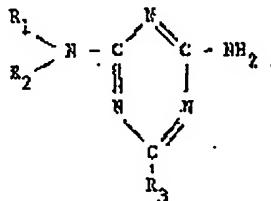
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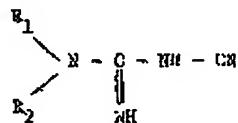
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The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. A process for the preparation of a compound of the formula:



in which: R_1 is an alkyl group of 2 to 4 carbon atoms, cyclohexyl, phenyl or phenyl substituted by fluoro, chloro, halo, mercapto, trifluoromethyl, methoxy, nitro or methyl; R_2 is a hydrogen atom, methyl or ethyl; and R_3 is pyridyl, an alkyl group of 1 to 5 carbon atoms, phenyl, *p*-isobutylbenzyl, *p*-isobutyl- α -methylbenzyl, *p*-tolyl, vinyl, hydroxyl or carboxyl, which process comprises reacting a substituted dicyanamide of the general formula:



in which R_1 and N_2 have the same meaning as above, with a nitrile having the general formula:



in which R_3 is pyridyl, an alkyl group of 1 to 5 carbon atoms, phenyl, *p*-isobutylbenzyl, *p*-isobutyl- α -methyl benzyl, *p*-furyl or vinyl, in the presence of a basic compound.

2. A process according to claim 1, wherein said substituted dicyandiamide is: N-(n-butyl)dicyandiamide; N-isobutylidicyandiamide; N-vinylidicyandiamide; N-(n-pentenyl)dicyandiamide; N-cyclohexylidicyandiamide; N-cycloheptylidicyandiamide; N-(*p*-bromophenyl)dicyandiamide; N-(*p*-fluorophenyl)dicyandiamide; N-(*n*-methylbenzyl)dicyandiamide; N-(*p*-chlorophenyl)dicyandiamide; N-phenethylidicyandiamide; N-(4-pyridyl)-dicyandiamide; N-(5-isouquinolyl)dicyandiamide; N-ethyl-N-n-butylidicyan-diamide; N-ethyl-N-phenylidicyandiamide; N-ethyl-N-(*p*-chlorophenyl)-

dicyanamide; N,N-diallyldicyanamide; N-(2,5-dichlorophenyl)dicyanamide; N-methyl-N-(n-trifluoromethylphenyl)dicyanamide; or N-(2,5-dimethoxyphenyl)dicyanamide.

3. A process according to claim 1, in which said nitrile is: acetonitrile; propionitrile; n-butyronitrile; isobutyronitrile; acrylonitrile; allycyanide; benzonitrile; p-methylbenzonitrile; p-chlorobenzonitrile; m-nitrobenzonitrile; o-naphthylcyanide; benzylcyanide; p-isobutylbenzylcyanide; p-isobutyl-o-methylbenzylcyanide; 3-cyanopyridine; or 4-cyanopyridine.

4. A process according to claim 2 in which said nitrile is: acetonitrile; propionitrile; n-butyronitrile; isobutyronitrile; acrylonitrile; allycyanide; benzonitrile; o-methylbenzonitrile; p-chlorobenzonitrile; m-nitrobenzonitrile; o-naphthylcyanide; benzylcyanide; p-isobutylbenzylcyanide; p-isobutyl-o-methylbenzylcyanide; 3-cyanopyridine; or 4-cyanopyridine.

5. A process according to claims 2, 3 or 4 in which said basic compound is selected from the group consisting of alkali carbonates, alkali hydroxides, metal alcoholates, alkali amides, tertiary amines and quaternary ammonium salts.

6. A process according to claims 2, 3 or 4 in which said carbonyl derivative is carbonic acid ester and in which said basic compound is a sodium alcoholate.

7. A process according to claims 2, 3 or 4 in which said carbonyl derivative is carbonic acid ester and in which said sodium alcoholate is sodium methoxide.

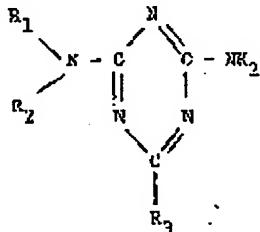
8. A process according to claims 1 or 2 carried out in the presence of one or more solvents selected from hydrocarbons, ethers, ketones, alcohols or other organic solvents, selected from methyl cellosolve, ethyl cellosolve, dioxane or butanol.

9. A process according to claims 3 or 4 carried out in the presence of one or more solvents selected from hydrocarbons, ethers, ketones, alcohols or other organic solvents, selected from methyl

cellosolve, ethyl cellosolve, dioxane or butanol.

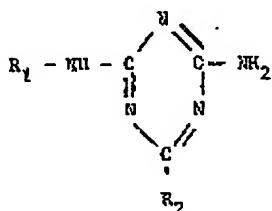
10. A process according to claim 1 including the step of forming pharmaceutically acceptable acid addition salts by reaction with an acid selected from the group comprising hydrochloric acid, hydrobromic acid, sulphuric acid, nitric acid, phosphoric acid, perchloric acid, formic acid, acetic acid, propionic acid, oxalic acid, succinic acid, glycolic acid, nicotinic acid, tartaric acid, maleic acid, malic acid, lactic acid, pimelic acid, citric acid, ascorbic acid, methanesulphonic acid, salicylic acid, benzoic acid or cyclohexanesulphonic acid.

11. A compound selected from (a) those of the formula:



in which R_1 is an alkyl group of 2 to 4 carbon atoms, cyclohexyl, phenyl or phenyl substituted by fluoro, chloro, iodo, mercapto, trifluoromethyl, ethoxy or methyl, R_2 is a hydrogen atom, methyl or ethyl and R_3 is pyridyl, an alkyl group of 1 to 5 carbon atoms, phenyl, p-isobutylbenzyl, p-isobutyl- α -methylbenzyl, p-tolyl, vinyl, hydroxyl or carboxyl, whatever prepared by the process of claim 1 or by its obvious chemical equivalents; and (b) pharmaceutically acceptable acid addition salts of a compound of the formula 1, whenever prepared by the process of claim 10 or by its obvious chemical equivalents.

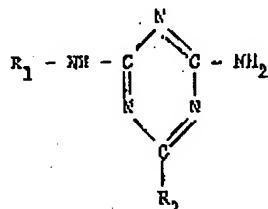
12. A compound of the formula



wherein R_1 represents phenyl substituted by fluoro, chloro, iodo,

mercapto, trifluoromethyl, phenyl, ethoxy, nitro or methyl and R₂ represents pyridyl, an alkyl group of 1 to 3 carbon atoms, phenyl, p-isobutylbenzyl or p-isobutyl- α -methylbenzyl whenever prepared by the process of claim 1 or by its obvious chemical equivalents.

13. A pharmaceutically acceptable solid addition salt of a compound of the formula



wherein R₁ represents phenyl substituted by fluoro, chloro, indo, morcepto, trifluoromethyl, phenyl, ethoxy, nitro or methyl and R₂ represents pyridyl, an alkyl group of 1 to 3 carbon atoms, phenyl, p-isobutylbenzyl, or p-isobutyl- α -methylbenzyl whenever prepared by the process of claim 1 or by its obvious chemical equivalents, and in which the acid is: hydrochloric acid, hydrobromic acid, sulphuric acid, nitric acid, phosphoric acid, perchloric acid, formic acid, acetic acid, propionic acid, oxalic acid, succinic acid, glycolic acid, nicotinic acid, tartaric acid, maleic acid, malic acid, lactic acid, pamoic acid, citric acid, ascorbic acid, methanesulphonic acid, malic acid, benzoic acid or cyclohexanesulphonic acid, whenever prepared or produced by the process of claim 10 or by its obvious chemical equivalent.

14. As a compound of claim 12, 2-amino-4-(N-ethylanilino)-6-(3-pyridyl)-1,3,5-triazine; 2-amino-4-(N-ethylanilino)-6-ethyl-1,3,5-triazine; 2-amino-4-(p-chloroanilino)-6-phenyl-1,3,5-triazine; 2-amino-4-(p-chloroanilino)-6-methyl-1,3,5-triazine; 2-amino-4-(n-butyl-amino)-6-(3-pyridyl)-1,3,5-triazine; 2-amino-4-cyclohexylamino-6-(p-tolyl)-1,3,5-triazine; 2-amino-4-(p-bromoanilino)-6-vinyl-1,3,5-triazine; 2-amino-4-(p-fluoroanilino)-6-(n-propyl)-1,3,5-triazine; 2-amino-4-(m-trifluoromethylanilino)-6-(p-isobutylbenzyl)-1,3,5-triazine; 2-amino-4-cyclohexylamino-6-ethyl-1,3,5-triazine; 2-amino-4-(p-fluoro-

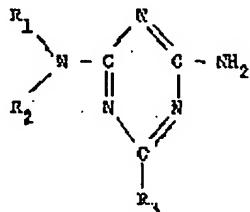
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anilino)-6-ethyl-1,3,5-triazine; 2-amino-4-(*p*-butylamino)-6-(*p*-isobutyl-henzy1)-1,3,5-triazine; 2-amino-4-(*p*-bromosulphino)-6-ethyl-1,3,5-triazine; and 2-amino-4-(*p*-methylsulphino)-6-methyl-1,3,5-triazine; whenever prepared by the process of claims 2, 3 or 4 or by their obvious chemical equivalents.

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This invention relates to a process for preparing novel *s*-triazine derivatives and to the novel *s*-triazine derivatives so formed.

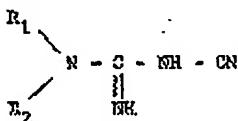
According to one aspect, therefore, the present invention provides novel *s*-triazine derivatives having the following general formula:



1.0 In which: R_1 is an alkyl group of 2 to 4 carbon atoms, cyclohexyl, phenyl or phenyl substituted by fluoro, chloro, iodo, mercapto, trifluoromethyl, ethoxy, nitro or methyl; R_2 is a hydrogen atom, methyl or ethyl; and R_3 is pyridyl, an alkyl group of 1 to 5 carbon atoms, phenyl, *p*-isobutylbenzyl, *p*-isobutyl- α -methylbenzyl, *p*-tolyl, vinyl, hydroxyl or carboxyl, as well as pharmaceutically acceptable acid addition salts of these derivatives.

The invention also provides in another of its aspects, a process for producing such *s*-triazine derivatives which comprises reacting a substituted dicyanadiimide of the general formula:

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in which R_1 and R_2 have the same meaning as above, with a nitrile having the general formula



in which R_3 is pyridyl, an alkyl group of 1 to 5 carbon atoms, phenyl, *p*-isobutylbenzyl, *p*-isobutyl- α -methylbenzyl, *p*-tolyl or vinyl, in the presence of a basic compound.

By another aspect of this invention, pharmaceutically acceptable acid addition salts of such novel *s*-triazine are provided by reaction of the *s*-triazine with an acid selected from the group comprising hydrochloric acid, hydrobromic acid, sulphuric acid, nitric acid.

phosphoric acid, perchloric acid, formic acid, acetic acid, propionic acid, oxalic acid, succinic acid, glycolic acid, nicotinic acid, tartaric acid, maleic acid, malic acid, lactic acid, pamoic acid, citric acid, ascorbic acid, methanesulphonic acid, salicylic acid, benzoic acid or cyclohexanesulphonic acid.

It will be further understood that R_3 will sometimes change from one radical into another during the reaction for preparing the α -triazine derivatives or their salts; for example, R_3 may change from an alkoxycarboxyl radical into a carboxyl radical, and from a substituted alkyl radical into an hydroxyl radical.

The compounds of a main aspect of the present invention may be used in pharmaceutical compositions and possess a wide range of bioactivity in, for example, birds and mammals including humans. Its bioactivity remarkably increases the secretion of induced corticoid in the hormone system.

Moreover, the starting materials used in the processes of other aspects of the present invention, namely, the compounds of substituted dicyandiamide, and the nitrile are comparatively inexpensive and are available in large quantities; also, the yield of the process is excellent.

Examples of suitable substituted dicyandiamides which can be used in the process of one aspect of the present invention include: N -(*n*-butyl)dicyandiamide; N -isobutyldicyandiamide; N -vinyldicyandiamide; N -(*n*-pentenyl)dicyandiamide; N -cyclohexyldicyandiamide; N -cycloheptyldicyandiamide; N -(*p*-bromophenyl)dicyandiamide; N -(*p*-fluorophenyl)dicyandiamide; N -(*o*-methylbenzyl)dicyandiamide; N -(*p*-chlorophenyl)dicyandiamide; N -phenethylidicyandiamide; N -(4-pyridyl)dicyandiamide; N -(5-isoquinolyl)dicyandiamide; N -ethyl- N -(*n*-butyl)dicyandiamide; N -ethyl- N -phenyldicyandiamide; N -ethyl- N -(*p*-chlorophenyl)dicyandiamide; N , N -diethylidicyandiamide; N -(2,5-dichlorophenyl)dicyandiamide; N -methyl- N -(*m*-trifluoromethylphenyl)dicyandiamide; and N -(2,5-diethoxyphenyl)dicyandiamide.

Examples of suitable nitriles which can be used in the process of one aspect of the present invention include: acetonitrile; propionitrile; *n*-butyronitrile; isobutyronitrile; acrylonitrile; allylcyanide; hexanitrile; *o*-methylbenzonitrile; *n*-chlorobenzonitrile; *m*-nitrobenzonitrile; *o*-naphthylcyanide; benzylcyanide; *p*-isobutylbenzylcyanide; *p*-isobutyl-*o*-methylbenzylcyanide; 3-cyanopyridine; and 4-cyanopyridine.

In the process of one aspect of this invention, inorganic or organic compounds such as, for example, alkali carbonates, alkali 10 hydroxides, metal alcoholates, alkali amides, tertiary amines, quaternary ammonium salts or the like may be useful as the basic compounds, in the presence of which the reaction between the substituted dicyandiamide and the nitrile is conducted. It is possible that the reaction will take place in the absence of a solvent; however, generally the reactions may better be carried out in the presence of the solvent. Hydrocarbons, ethers, ketones, alcohols and/or the other organic solvents may be used as the solvent, provided that the solvent does not interfere with the reaction; methyl cellosolve, ethyl cellosolve, dioxene or butanol are particularly preferred. In the case where an excess 20 of the nitrile is used, the solvent need not be used in the reaction. The reaction may be effected at a temperature of 50 to 200°C., but preferably near the temperature of this reflux. The reaction will normally take from 20 minutes to 24 hours to reach completion, at which time the *s*-triazine derivatives can be obtained in high yields.

The basic compound may be selected from the group consisting of alkali carbonates, alkali hydroxides, metal alcoholates, alkali amides, tertiary amines and quaternary ammonium salts, and the carbonyl derivative may be carbonylic acid ester in which the basic compound is a sodium alcoholate.

30 The *s*-triazine can be used in the form of a free base or as a salt produced by reacting the free base and an acid, for example, hydrochloric acid, hydrobromic acid, sulphuric acid, nitric acid,

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phosphoric acid, perchloric acid, formic acid, acetic acid, propionic acid, oxalic acid, succinic acid, glycolic acid, nicotinic acid, tartaric acid, maleic acid, malic acid, lactic acid, pantoic acid, citric acid, ascorbic acid, methanesulphonic acid, salicylic acid, benzoic acid, or cyclohexanesulphamic acid or other pharmaceutically acceptable acids.

The utility of various aspects of this invention is shown hereinafter in the

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pharmaceutical data.

In Table 1 below, R_1 , R_2 and R_3 of the triazines obtained in the following examples and of other triazines obtained by similar processes are shown. Table 1 also provides the melting points thereof and their code numbers, provided with "M" signs.

Table 1

| Product | R_1 > N < R_2 | R_3 | Melting point (°C) |
|---------|--|---|--------------------|
| 10 | M0626 <i>n</i> -butylamino | <i>p</i> -isobutylbenzyl | 99.5-101 |
| | M0632 <i>n</i> -butylamino | 3-pyridyl | 144.5-145.5 |
| | M1403 <i>o</i> -methylanilino | ethyl | 196-198 |
| | M1431 <i>o</i> -methylanilino | 4-pyridyl | 193-194 |
| | M1602 <i>p</i> -methylanilino | methyl | 204-205 |
| | M1613 <i>p</i> -methylanilino | phenyl | 156-158 |
| | M1631 <i>p</i> -methylanilino | 4-pyridyl | 200-201 |
| | M1632 <i>p</i> -methylanilino | 3-pyridyl | 200-201 |
| | M1702 <i>p</i> -fluoroanilino | methyl | 203-204 |
| | M1703 <i>p</i> -fluoroanilino | ethyl | 160-161 |
| 20 | M1704 <i>p</i> -fluoroanilino | <i>n</i> -propyl | 137-138 |
| | M1705 <i>p</i> -fluoroanilino | isopropyl | 148-149 |
| | M1804 <i>p</i> -chloroanilino | <i>n</i> -propyl | 137-138 |
| | M1813 <i>p</i> -chloroanilino | phenyl | 113-115 |
| | M1827 <i>p</i> -chloroanilino | <i>p</i> -isobutyl- <i>p</i> -(<i>m</i> -methylbenzyl) | 179-182 |
| | M1832 <i>p</i> -chloroanilino | 3-pyridyl | 223-224 |
| | M2104 <i>o</i> -mercaptoaniline | <i>n</i> -propyl | 164-166 |
| 30 | M2106 <i>o</i> -mercaptoaniline | <i>n</i> -butyl | 156 |
| | M2107 <i>o</i> -mercaptoaniline | <i>n</i> -pentyl | 135 |
| | M2113 <i>o</i> -mercaptoaniline | phenyl | 168-169 |
| | M2116 <i>o</i> -mercaptoaniline | <i>p</i> -tolyl | 160 |
| | M2131 <i>o</i> -mercaptoaniline | 4-pyridyl | 139-141 |
| | M2205 <i>m</i> -trifluoromethylanilino | <i>t</i> o ² propyl | 108-109 |

(continued)

| Product | $\begin{matrix} R_1 \\ \diagup \\ R_2 \end{matrix} > R -$ | $R_3 -$ | Melting point (°C) |
|---------|---|-----------|--------------------|
| M2231 | <u>m</u> -trifluoromethylanilino | 4-pyridyl | 229-230 |
| M2232 | <u>m</u> -trifluoromethylanilino | 3-pyridyl | 220-221 |
| M2502 | 2,5-diethoxyanilino | methyl | 178-180 |
| M2504 | 2,5-diethoxyanilino | n-propyl | 147-148 |
| M2803 | cyclohexylamino | ethyl | 147-149 |
| M2816 | cyclohexylamino | p-tolyl | 152-153.5 |
| 10 | M5103 <u>N</u> -ethylanilino | ethyl | 136 |
| | M5132 <u>N</u> -ethylanilino | 3-pyridyl | 185-186 |

The *s*-triazine derivatives (I) obtained by the processes of aspects of this invention act on the hormone system, especially the system of the diencephalon, the pituitary gland and the adrenal gland, and remarkably increase the secretion of the internally induced corticoid, mainly glucocorticoid.

The experimental results concerning the toxicity, the increased secretion of glucocorticoid, and the pharmaceutical effect similar to that of adrenal cortex hormone are shown below when *s*-triazine derivatives (I) are administered.

Table 2 shows the result of the numerical calculation of the LD₅₀ obtained by means of male mice. From the Table, it is seen that such *s*-triazines have very low toxicity, and are applicable to a very wide range of medical treatments.

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Table 2

| Product | LD ₅₀ (mg/kg) | Use | Product | LD ₅₀ (mg/kg) | Use |
|---------|--------------------------|------|---------|--------------------------|------|
| M1431 | 2700 | p.o. | X2104 | 100 | i.v. |
| M1602 | 750 | p.o. | M2205 | > 5000 | p.o. |
| M1613 | > 3000 | p.o. | M2231 | > 3000 | p.o. |
| M1702 | 1000 | p.o. | M2232 | > 3000 | p.o. |
| M1703 | 1000 | p.o. | M2502 | > 5000 | p.o. |
| M1704 | 2000 | p.o. | | > 300 | i.v. |
| X1705 | 2000 | p.o. | X2504 | > 5000 | p.o. |
| M1804 | 1200 | p.o. | | > 500 | i.v. |
| M1832 | > 5000 | p.o. | | | |

(Remarks) p.o. stands for oral administration
 i.v. stands for intravenous administration

Most of the s-triazine derivatives (1) of aspects of this invention promote the secretion of internally induced corticoid. Measurements were regularly made of the concentration of corticosterone, in the blood subsequent to the oral administration thereof to rats.

The results of the measurements are shown in Table 3.



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Table 3

| Product | Dose (mg/kg) | Corticosterone (μg/ml blood plasma) | | | | | Total |
|---------|-----------------|-------------------------------------|------------------------|------------------------|------------------------|---------------------------|--------------------------|
| | | Value shown 1 hour | Value shown 3 hours | Value shown 5 hours | Value shown 7 hours | after admin- istration | after admin- stration |
| X1403 | 600 | 68 | 66 | 102 | 107 | 343 | |
| M1431 | 200 | 70 | 110 | 60 | 75 | 318 | |
| M1602 | 100 | 66 | 54 | 51 | 70 | 241 | |
| M1613 | 600 | 65 | 110 | 75 | 65 | 315 | |
| 10 | M1702 | 200 | 64 | 65 | 54 | 40 | 223 |
| | M1703 | 200 | 49 | 65 | 50 | 66 | 230 |
| | M1704 | 400 | 61 | 61 | 64 | 61 | 247 |
| | X1705 | 400 | 60 | 69 | 67 | 30 | 246 |
| | M1832 | 600 | 70 | 55 | 70 | 45 | 240 |
| | X2104 | 20 | 300 | 30 | 45 | 30 | 405 |
| | M2106 | 600 | 75 | 88 | 71 | 73 | 307 |
| | M2113 | 100 | - | 45 | 55 | 37 | 137 |
| | M2136 | 44 | 44 | 47 | 28 | 53 | 172 |
| | M2131 | 34 | 65 | 52 | 70 | 81 | 298 |
| 20 | M2205 | 200 | 75 | 67 | 45 | 47 | 234 |
| | H2231 | 600 | 28 | 32 | 29 | 29 | 118 |
| | M2502 | 600 | 67 | 57 | 43 | 71 | 238 |
| | Control | 0 | 46 | 4 | 22 | 16 | 88 |

ACTH (adrenocorticotropichormone) and corticoid have the effect of increasing hepatic glycogen. Table 4 shows the degree of settlement of hepatic glycogen that is measured when the α -triazine derivatives (I) of aspects of this invention are administered to rats in a dose of 25 μg/kg and 5 mg/kg respectively.

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Table 4

| Product | Dose | Quantity of Hepatic Glycogen (mg/g Liver) | |
|----------------|------|---|-------------|
| | | 25 mg/kg | 5 mg/kg |
| M1403 | | 0.747±0.257 | 0.537±0.652 |
| K1613 | | 2.017±0.455 | 0.526±0.055 |
| M1703 | | 1.705±0.401 | 1.468±0.958 |
| M1704 | | 1.011±0.458 | 1.234±0.569 |
| M1705 | | 1.583±0.541 | 0.574±0.621 |
| 10 M1804 | | 3.436±1.140 | 0.530±0.014 |
| M1832 | | 1.931±0.543 | 0.700±0.385 |
| M2104 | | | 5.007±1.226 |
| M2116 | | | 1.608±0.834 |
| M2205 | | 1.771±0.478 | 0.559±0.052 |
| X2231 | | 1.072±0.163 | 1.361±0.422 |
| X2232 | | 1.682±0.555 | 1.049±0.517 |
| Hydrocortisone | | | 1.728±0.341 |
| Control | | 0.527±0.106 | 0.432±0.129 |

20 Table 5 shows the effect on the thymus gland, the adrenal gland and the spleen which effects are measured after oral administration to rats.

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Table 5

| Product | Dose (mg/kg) | Organ Gain (%) | | |
|----------------|-----------------|-----------------|------------------|--------|
| | | Thymus Gland | Adrenal Gland | Spleen |
| M1431 | 50 | -2.6 | 79.5 | -14.6 |
| | 100 | -10.5 | 40.2 | -13.8 |
| M1632 | 50 | -16.0 | 50.4 | -12.4 |
| | 100 | -35.9 | 100.0 | -20.5 |
| 10 M1702 | 50 | -23.8 | 37.3 | 10.4 |
| | 100 | -22.0 | 38.6 | 6.1 |
| M1704 | 50 | -15.8 | 43.1 | 10.1 |
| | 100 | -19.4 | 35.3 | 4.9 |
| M1705 | 50 | -3.9 | 28.1 | 41.0 |
| | 100 | -11.9 | 34.6 | 18.0 |
| M1832 | 50 | -5.9 | 32.5 | -32.5 |
| | 100 | -7.2 | 53.8 | -21.6 |
| M2106 | 31 | -3.9 | 64.1 | -1.4 |
| M2116 | 11 | -8.8 | 35.0 | -23.0 |
| 20 | 22 | 2.0 | 47.9 | -11.8 |
| | 8 | -15.0 | 28.2 | -35.4 |
| | 16 | 4.6 | 87.2 | -7.3 |
| Hydrocortisone | 50 | -74.8 | -39.7 | 24.1 |

Corticoid has a very strong anti-inflammation effect. The administration of the *s*-triazine derivatives (1) of aspects of this invention leads to an increase in the secretion of internally induced corticoid, and an anti-inflammation effect can be expected. Table 6 shows the results of oral administration thereof to rats.

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Table 6

| Product | Dose (mg/kg) | Suppression (%) | | | |
|----------------|-----------------|-----------------------------------|-----|------------------------------|------------------------------|
| | | Cotton-pellet Glucuronidase Assay | | Glaucuronidase Wet Weight | Glaucuronidase Dry Weight |
| | | | | | |
| X1403 | 100 | -2 | -28 | 20 | |
| | 50 | 30 | 31 | 68 | |
| X1431 | 100 | 3 | 14 | 70 | |
| | 50 | 25 | 29 | 28 | |
| 10 X1602 | 75 | 11 | 46 | 57 | |
| | 38 | -1 | 33 | 25 | |
| M1702 | 100 | -2 | 27 | 59 | |
| | 50 | 13 | 19 | 46 | |
| X1704 | 100 | 28 | 37 | 74 | |
| | 50 | 28 | 37 | 39 | |
| M1705 | 100 | 5 | 36 | 63 | |
| | 50 | 16 | 8 | 55 | |
| X2104 | 20 | 18 | 27 | 66 | |
| | 10 | 18 | 40 | 29 | |
| 20 X2113 | 50 | 20 | 34 | 27 | |
| | 25 | 39 | 54 | 43 | |
| M2116 | 22 | 37 | 44 | 11 | |
| | 11 | 28 | 32 | 33 | |
| X2131 | 17 | 33 | 23 | 1 | |
| | 9 | 21 | 17 | 1 | |
| Corticosterone | 50 | | | 32 | |
| | 10* | 21 | 23 | | |
| Hydrocortisone | 50 | 41 | 41 | 53 | |
| | 10* | 44 | 48 | | |

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*Intravenous administration

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The oral or intravenous administration of the s-triazine derivatives (I) of aspects of this invention to rats, rabbits and dogs will result in a remarkable increase in the quantity of 17-OHCS in the blood and urine as compared to the group of controls. If the s-triazine derivatives of aspects of this invention are used together with a glucocorticoid, the hormone effect thereof is remarkably increased.

From the above-described pharmacological experiments, the following two effects can be noted concerning the s-triazine derivatives (I) of aspects of this invention:

10 (1) Through the effect on the pituitary system and on the adrenal system, it causes an increase in the biosynthesis of the hormone, especially glucocorticoid.

(2) Through the participation in the function of the hormone, it intensifies the performance of the hormone.

ACTH and corticoid have a large variety of physiological and pharmacological effects, and thus they are used for various medical purposes; however, they are not free from many secondary ill effects. The most serious disadvantage of the continuous administration of corticoid is believed to be a decline in the performance of the adrenal cortex and a withdrawal syndrome.

20 ACTH shows the same effect as in the case of the administration of steroid, and one of its advantages is that the adrenal cortex performance is not decreased and well-balanced secretion of corticoid from the adrenal cortex is not upset. However, it has serious disadvantages in that it must be used exclusively by injection, it is extremely expensive, and it is not free from cases of death from shock. Thus its clinical application is radically restricted.

30 The merit of the novel s-triazine compounds of aspects of this invention lies in the removal of the disadvantages of ACTH or corticoid while providing the desirable effects of such compounds.

Because of the effect of the s-triazine compounds of aspects of this invention in increasing the secretion of internally induced

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corticoid, one can expect from such compounds the same effect as from the administration of ACTH or corticoid in the same of the following diseases:

- Kidney disease
- Bronchial asthma
- Chronic arthrorheumatism
- Rheumatic fever
- Chronic hepatitis
- Allergic disease
- 10 Malignant lymphoma
- Spinitis

and many other diseases that are believed to be adapted to the administration of steroid agent.

The novel α -triazine compounds (I) of aspects of the present invention can be applied in the form of any suitable medicinal composite in combination with other medicines as the case may be. They can be taken orally or otherwise. They can be administered in any pharmaceutically possible form, for example, powders, capsules, pellets, granules, injections or suppositories.

20 From the data given above, it is noted that the α -triazine derivatives of aspects of the present invention provide a new important substitute medicine in the field of the adrenal cortex steroid therapeutics.

Aspects of the present invention are illustrated by the following examples:

Example 1

2-Amino-4-(N-ethylaniline)-6-(3-pyridyl)-1,3,5-triazine

18.8 grams of N-ethyl- α -phenyldicyandiamide and 10.5 grams of 3-cyanopyridine were added to a solution of 4 grams of potassium hydroxide in 60 ml of ethyl cellosolve and the mixture was refluxed under stirring for 3 hours. The solution was then poured into about 500 ml of hot water and the white crystals precipitated were collected by

filtration and recrystallized from acetonitrile. 19.5 grams of 2-amino-4-(N-ethylanilino)-6-(3-pyridyl)-1,3,5-triazine having a melting point of 185 ~ 186°C. were thus obtained.

Elementary analysis for $C_{16}H_{16}N_6$:

Theoretical: C 65.74%, H 5.52%, N 28.75%

Experimental: C 65.53%, H 5.60%, N 29.00%

Example 2

2-Amino-4-(N-ethylanilino)-6-ethyl-1,3,5-triazine

16.9 grams of N-ethyl-N-phenyldicyandiamide and 6.6 grams of acetonitrile were added to a solution of 3.2 grams of potassium hydroxide in 40 ml of methyl cellosolve and the mixture was refluxed under stirring for 2.5 hours. The solution was then poured into 300 ml of hot water and the white crystals precipitated were collected by filtration and recrystallized from acetonitrile. 13.8 grams of 2-amino-4-(N-ethylanilino)-6-ethyl-1,3,5-triazine having a melting point of 136°C. were thus obtained.

Elementary analysis for $C_{13}H_{17}N_5$:

Theoretical: C 64.18%, H 7.04%, N 28.78%

Experimental: C 64.49%, H 7.22%, N 28.76%

20 This 2-amino-4-(N-ethylanilino)-6-ethyl-1,3,5-triazine were recrystallized from hydrochloric acid and the monohydrochloride was thus obtained.

Elementary analysis for $C_{13}H_{18}N_5Cl$:

Theoretical: C 55.81%, H 6.49%, N 25.03%, Cl 12.67%

Experimental: C 56.07%, H 6.48%, N 24.99%, Cl 12.82%

Example 3

2-Amino-4-(p-chloroanilino)-6-phenyl-1,3,5-triazine

3.0 grams of N-(p-chlorophenyl)-dicyandiamide and 1.6 grams of benzonitrile were added to a solution of 1.0 gram of sodium methylate in 30 ml of ethyl cellosolve and the mixture was refluxed under stirring for 2 hours. 3 ml of water was then added to this solution and the mixture was then poured into 70 ml of water and the white crystals precipi-

tated were collected by filtration and recrystallized from α -butanol.

2.4 grams of 2-amino-4-(p -chloroanilino)-6-phenyl-1,3,5-triazine having a melting point of 114 - 115°C. were thus obtained.

Elementary analysis for $C_{13}H_{12}N_3Cl$:

Theoretical: C 60.51%, H 4.06%, N 23.52%, Cl 11.91%

Experimental: C 60.78%, H 4.13%, N 23.80%, Cl 11.85%

When 1 equivalent of methanesulfonic acid was dropped into a dioxane solution of this 2-amino-4-(p -chloroanilino)-6-phenyl-1,3,5-triazine under cooling and stirring, the methanesulfonate was obtained.

10 Elementary analysis for $C_{16}H_{16}N_3ClS$:

Theoretical: C 48.79%, H 4.09%, N 17.78%

Experimental: C 48.51%, H 4.26%, N 17.38%

Example 4

2-Amino-4-(p -chloroanilino)-6-methyl-1,3,5-triazine

2.0 grams of K-(p -chlorophenyl)-dicyanamide, 20 ml of acetonitrile and 1.5 grams of potassium hydroxide were heated under stirring. In this case the potassium hydroxide generally dissolves in the mixture. After refluxing for 5 hours, the solution was poured into hot water and the white crystals precipitated were collected by filtration and recrystallized from α -butanol. 1.3 grams of 2-amino-4-(p -chloroanilino)-6-methyl-1,3,5-triazine having a melting point of 196 - 197°C. were thus obtained.

Elementary analysis for $C_{10}H_{10}N_3Cl$:

Theoretical: C 50.96%, H 4.28%, N 29.72%, Cl 15.04%

Experimental: C 50.71%, H 4.09%, N 30.30%, Cl 14.85%

When ethanol containing 1 equivalent of hydrochloric acid was added to an ethanol solution of this 2-amino-4-(p -chloroanilino)-6-methyl-1,3,5-triazine, the monohydrochloride was obtained. When 1 equivalent of acetylbenzaldehyde was used in the same way, the monoacetylbenzalicyclic addition salt was obtained.

Example 5

2-Amino-4-(n -butylinino)-6-(3-pyridyl)-1,3,5-triazine

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25.2 grams of N-n-butylidicyandiamide and 18.8 grams of 3-cyano-pyridine were added to a solution of 10.8 grams of potassium hydroxide in 100 ml of ethyl cellulose and the mixture was refluxed under stirring for 3 hours. The solution was then poured into 500 ml of hot water and the white crystals precipitated were collected by filtration and recrystallized from acetonitrile. 28.6 grams of 2-amino-4-(n-butylamino)-6-(3-pyridyl)-1,3,5-triazine having a melting point of 144.5 - 145.5°C. were thus obtained.

Elementary analysis for $C_{12}H_{16}N_6$:

Theoretical: C 59.00%, H 6.60%, N 34.40%

Experimental: C 58.84%, H 6.62%, N 34.75%

Example 6

2-amino-4-cyclohexylamino-6-(p-tolyl)-1,3,5-triazine

33.0 grams of N-cyclohexylidicyandiamide and 23.4 grams of p-methylbenzonitrile were added to a solution of 10 grams of potassium hydroxide in 100 ml of methyl cellulose and the mixture was refluxed under stirring for 2 hours. The solution was then poured into 500 ml of hot water and the white crystals precipitated were collected by filtration and recrystallized from n-butanol. 40.0 grams of 2-amino-4-cyclohexylamino-6-(p-tolyl)-1,3,5-triazine having a melting point of 152 - 153.5°C. were thus obtained.

Elementary analysis for $C_{15}H_{21}N_5$:

Theoretical: C 67.82%, H 7.47%, N 24.71%

Experimental: C 68.00%, H 7.44%, N 24.85%

Example 7

2-Amino-4-(p-bromanilino)-6-vinyl-1,3,5-triazine

4.3 grams of N-(p-bromophenyl)dicyandiamide and 1.0 gram of acrylonitrile were added to a solution of 0.8 gram of potassium hydroxide in 20 ml of ethyl cellulose and the mixture was refluxed under stirring for 3 hours. After cooling, water was added to this solution and the mixture was then extracted with chloroform. After distilling off the chloroform, the residue was recrystallized from acetonitrile.

2.7 grams of 2-amino-4-(*p*-bromoanilino)-6-vinyl-1,3,5-triazine having a melting point of 122 - 124°C. were thus obtained.

Elementary analysis for $C_{11}H_{10}N_5Br$:

Theoretical: C 45.23%, H 3.45%, N 23.97%

Experimental: C 45.20%, H 3.69%, N 23.82%

Example 8

2-Amino-4-(*p*-fluoroanilino)-6-(*n*-propyl)-1,3,5-triazine

33.8 grams of *N*-(*p*-fluorophenyl)dicyandiamide and 13.1 grams of *n*-butyronitrile were added to a solution of 5 grams of potassium hydroxide in 100 ml of ethyl cellosolve and the mixture was refluxed under stirring for 3 hours. The solution was then poured into 500 ml of hot water and the white crystals precipitated were collected by filtration and recrystallized from a mixed solution of ethanol and water. 27.6 grams of 2-amino-4-(*p*-fluoroanilino)-6-(*n*-propyl)-1,3,5-triazine having a melting point of 137 - 138°C. were thus obtained.

Elementary analysis for $C_{12}H_{14}N_5F$:

Theoretical: C 58.29%, H 5.71%, N 28.32%, F 7.68%

Experimental: C 57.94%, H 5.99%, N 28.17%, F 7.41%

Example 9

2-Amino-4-(*m*-trifluoromethylanilino)-6-(*p*-isobutylbenzyl)-1,3,5-triazine

25.0 grams of *m*-aminobenzenotrifluoride and 13 grams of dicyandiamide were dissolved in 62 ml of 10% hydrochloric acid. The solution was refluxed for 1 hour. After cooling, the precipitated *m*-trifluoromethylphenyldiguanide hydrochloride was collected by filtration, washed with water and dried.

14.1 grams of this *m*-trifluoromethylphenyldiguanide hydrochloride were added to a solution of 1.2 grams of metallic sodium in 70 ml of methanol and the mixture was stirred. 11.0 grams of ethyl *p*-isobutylphenylacetate were then added to the solution, which was left at room temperature for 72 hours. At the end of this time, water was added in an amount of twice the volume of the reactant solution, which was allowed to cool. Crystals precipitated thereby were collected by

filtration and recrystallized from a mixed solvent of ethanol and water. 11.6 grams of 2-amino-4-(*m*-trifluoromethylanilino)-6-(*p*-isobutylbenzyl)-1,3,5-triazine were thus obtained.

Elementary analysis for $C_{21}H_{22}N_5F_3$:

Theoretical: C 62.83%, H 5.52%, N 17.45%

Experimental: C 62.71%, H 5.50%, N 17.39%

Example 10

2-Amino-4-cyclohexylamino-6-ethyl-1,3,5-triazine

34.5 grams of cyclohexylamino hydrochloride and 21.5 grams of 10 dicyandiamide were uniformly ground together. The mixture was melted in oil bath at 150 - 160°C. and maintained at this temperature for about 30 minutes. It was then cooled, dissolved in hot methanol and the solution cooled. Cyclohexylbiguanide hydrochloride was thereby precipitated.

11.0 grams of this cyclohexylbiguanide hydrochloride were added to a solution of 1.2 grams of metallic sodium in 40 ml of methanol. 5.2 grams of ethyl propionate were then added and the mixture was stirred. After leaving the mixture at room temperature for 72 hours, water was added thereto in an amount twice the volume of the reacting 20 solution, to precipitate white crystals. The precipitated crystals were collected by filtration and recrystallized from a mixed solvent of ethanol and water. 8.4 grams of 2-amino-4-cyclohexylamino-6-ethyl-1,3,5-triazine having a melting point of 147 - 149°C. were thus obtained.

Elementary analysis for $C_{11}H_{18}N_5$:

Theoretical: C 59.97%, N 8.24%, N 31.79%

Experimental: C 60.28%, N 8.21%, N 31.84%

Example 11

2-Amino-4-(*p*-fluoranilino)-6-ethyl-1,3,5-triazine

80.5 grams of *p*-fluoraniline and 61.2 grams of dicyandiamide 30 were dissolved in 290 ml of 10% hydrochloric acid and the solution was refluxed for 1 hour. After cooling, *p*-fluorophenylbiguanide hydrochloride, which was precipitated, was collected by filtration and dried.

11.5 grams of this *p*-fluorophenyldiguanide hydrochloride were added to a solution of 1.5 grams of metallic sodium in 70 ml of methanol. 5.2 grams of ethyl propionate were then added and the mixture was stirred. After leaving the mixture at room temperature for 72 hours, water was added in an amount twice the volume of the solution and the mixture was allowed to cool. The crystals so precipitated were collected by filtration and recrystallized from *n*-butanol. 8.3 grams of 2-amino-4-(*p*-fluoroanilino)-6-ethyl-1,3,5-triazine having a melting point of 160 - 161°C. were thereby obtained.

18 Elementary analysis for $C_{11}H_{12}N_5F$:

Theoretical: C 56.64%, H 5.19%, N 30.03%

Experimental: C 56.49%, H 4.96%, N 30.00%

Example 12

2-amino-4-(*n*-butylamino)-6-(*p*-isobutylbenzyl)-1,3,5-triazine

50 grams of *n*-butylamine hydrochloride and 38.4 grams of dicyandiamide were uniformly mixed and then melted on an oil bath at a temperature of $130 \pm 5^\circ\text{C}$. The mixture was maintained at this temperature for about 4 hours and then cooled. After cooling the mixture was dissolved in hot methanol and again cooled, precipitating *n*-butyldiguanide hydrochloride.

20 9.7 grams of this *n*-butyldiguanide hydrochloride were added to a solution of 1.5 grams of metallic sodium in 50 ml of methanol. 11.0 grams of ethyl *p*-isobutylphenylacetate were added thereto and the mixture was stirred. After leaving the mixture for 72 hours, water was added thereto in an amount twice the volume of the reacting solution. Crystals were precipitated, were collected by filtration and were recrystallized from a mixed solvent of ethanol and water. 13.5 grams of 2-amino-4-(*n*-butylamino)-6-(*p*-isobutylbenzyl)-1,3,5-triazine having a melting point of 99.5 - 101°C. were thereby obtained.

30 Elementary analysis for $C_{18}H_{27}N_5$:

Theoretical: C 68.97%, H 6.68%, N 22.34%

Experimental: C 69.17%, H 6.79%, N 22.32%

Example 132-Amino-4-(*p*-bromoanilino)-6-ethyl-1,3,5-triazine

21 grams of *p*-bromoanilino hydrochloride and 8.4 grams of dicyandiamide were dissolved in 40 ml of water and the solution was refluxed for 1 hour. The solution was then cooled and the *p*-bromophenyl-diguanide hydrochloride thus precipitated was collected by filtration, washed with water and dried.

5.4 grams of this *p*-bromophenyl-diguanide hydrochloride were dissolved under stirring in a solution of 10 grams of caustic soda in 10 ml of water and 10 ml of dioxane and 5.1 ml of propionic anhydride was dropped into the solution at a temperature between 50 and 55°C. 1 hour after the completion of dropping, the crystals precipitated by addition of 70 ml of water were filtered and recrystallized from *n*-butanol. 4.4 grams of 2-amino-4-(*p*-bromoanilino)-6-ethyl-1,3,5-triazine having a melting point of 178 - 180°C. were thus obtained.

Example 142-Amino-4-(*p*-methylanilino)-6-methyl-1,3,5-triazine

14.4 grams of *p*-toluidine hydrochloride and 8.4 grams of dicyandiamide were dissolved in 40 ml of water and the solution was refluxed for 1 hour. The solution was then cooled and the *p*-methylphenyl-diguanide hydrochloride thus precipitated was collected by filtration, washed with water and dried.

4.2 grams of this *p*-methylphenyl-diguanide hydrochloride was dissolved under stirring in a solution of 10 grams of caustic soda in 10 ml of water and 10 ml of dioxane and 4 ml of acetic anhydride was dropped into the solution at a temperature between 50 and 60°C. 1 hour after the completion of the dropping, the crystals precipitated by addition of 70 ml of water were filtered and recrystallized from *n*-butanol. 3.2 grams of 2-amino-4-(*p*-methylanilino)-6-methyl-1,3,5-triazine having a melting point of 170 - 172°C. were thus obtained.

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